Article title	Effects of Forskolin and Organic Nitrate on Aggregation and Intracellular Cyclic Nucleotide Content in Human Platelets
Article identifier	030636239510005A
Authors	Anfossi_G Massucco_P Mularoni_E Cavalot_F Mattiello_L Trovati_M
Journal title	General Pharmacology
ISSN	0306-3623
Publisher	Elsevier USA
Year of publication	1994
Volume	25
Issue	6
Supplement	0
Page range	1093-1100
Number of pages	8
User name	Adonis
Cost centre	Development
PCC	$20.00
Date and time	Thursday, July 27, 2000 3:50:02 PM

L11 ANSWER 1 OF 3 MEDLINE
ACCESSION NUMBER: 95174112 MEDLINE
DOCUMENT NUMBER: 95174112 PubMed ID: 7869513
TITLE: Duplex ultrasonography after **prostaglandin** E1 injection of the **clitoris** in a case of hyperreactio luteinalis.
AUTHOR: Akkus E; Carrier S; Turzan C; Wang T N; Lue T F
CORPORATE SOURCE: Department of Urology, University of California School of Medicine, San Francisco 94143-0738.
SOURCE: JOURNAL OF UROLOGY, **(1995 Apr)** 153 (4) 1237-8.
Journal code: KC7; 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950407
Last Updated on STN: 19950407
Entered Medline: 19950329

AB We report an unusual case of persistent postpartum **clitorimegaly** due to ovarian hyperreactio luteinalis. Duplex ultrasonography of the **clitoris** after intracorporeal injection of **prostaglandin** E1 revealed marked **clitoral** erection and increased arterial flow, as in the penis.

L10 ANSWER 1 OF 4 MEDLINE
ACCESSION NUMBER: 2000095314 MEDLINE
DOCUMENT NUMBER: 20095314
TITLE: The pharmacology of sildenafil, a novel and selective inhibitor of phosphodiesterase (PDE) type 5.
AUTHOR: Wallis R M
CORPORATE SOURCE: Pfizer Central Research, Sandwich, Kent, UK.
SOURCE: NIPPON YAKURIGAKU ZASSHI. FOLIA PHARMACOLOGICA JAPONICA, (1999 Oct) 114 Suppl 1 22P-26P. Ref: 12
Journal code: F2X. ISSN: 0015-5691.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY WEEK: 20000403

AB Sildenafil (1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d]pyrimidin-5-yl) phenylsulphonyl]-4-methylpiperazine) has been shown to be an effective oral treatment for male **erectile** dysfunction. Sildenafil is a potent competitive inhibitor of PDE5 (IC50 3.5 nM) and is selective over PDE1 to 4 (80 to 19,000-fold) and retinal PDE6 (10-fold). Sildenafil enhanced **cGMP** accumulation driven with sodium nitroprusside in the corpus cavernosum of rabbits without affecting **cAMP** formulation. In the absence of nitric oxide drive, sildenafil had no functional effect on the human and rabbit isolated corpus cavernosum, but potently potentiated the relaxant effects of nitric oxide on these tissues. In the anaesthetised dog, sildenafil (ED50: 12 to 16 micrograms/kg i.v.) enhanced the increase in intracavernosal pressure induced by electrical stimulation of the pelvic nerve or intracavernosal injection of sodium nitroprusside in the absence of meaningful effects on blood pressure. Consistent with its mode of action, sildenafil potentiated the vasorelaxant effects of **glyceryl trinitrate** on rabbit isolated aortic rings. However, unlike milrinone, sildenafil had no inotropic effects on the dog isolated trabeculae carneae. Thus it is unlikely to have the deleterious effects on cardiac function associated with PDE3 inhibitors. As a consequence of inhibition of PDE6 in the retina, sildenafil (1 to 100 microM) altered the kinetics of the light response of the dog isolated retina. In the anaesthetised dog, sildenafil modified the a- and b-wave of the electroretinogram induced by a flash of blue light. These effects were proportional to plasma concentrations, were fully reversible and only occurred following plasma concentrations higher (approximately 30-fold) than those active on intracavernosal pressure. These studies have shown that sildenafil is a potent and selective inhibitor of PDE5. It enhances the effect of nitric oxide on the corpus cavernosum and has been shown to be an effective oral treatment of **erectile** dysfunction.

L8 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:290119 CAPLUS
DOCUMENT NUMBER: 120:290119
TITLE: Treating **sexual dysfunction** in animals using histamine H2 and H3 receptor agonists
INVENTOR(S): Nahoum Cesar, Roberto Dias
PATENT ASSIGNEE(S): Brazil
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9404120	A2	19940303	WO 1993-BR27	19930818	<--
WO 9404120	A3	19940526			
W: AT, AU, CA, CH, DE, DK, ES, GB, JP, KI, KR, LU, NL, NZ, PT, SE, US					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN					
BR 9203277	A	19940301	BR 1992-3277	19920821	<--
EP 655914	A1	19950607	EP 1993-918819	19930818	<--
R: AT, CH, DE, DK, ES, GB, LI, LU, NL, PT, SE					
AU 678996	B2	19970619	AU 1993-49371	19930818	
ZA 9306118	A	19950420	ZA 1993-6118	19930820	<--
US 5908853	A	19990601	US 1995-381945	19950215	
PRIORITY APPLN. INFO.:			BR 1992-3277	19920821	
			WO 1993-BR27	19930818	

OTHER SOURCE(S): MARPAT 120:290119

AB Histamine H2 and H3 receptor agonists are used as erectogenic agents in the treatment of male and **female sexual dysfunction**. All human subjects showed some degree of erectile response when submitted to Impromidine injection by the intracavernous route. Formulations with Impromidine hydrochlorides are given.

L13 ANSWER 1 OF 5 MEDLINE
ACCESSION NUMBER: 96263638 MEDLINE
DOCUMENT NUMBER: 96263638
TITLE: Intracavernous alprostadil. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in **erectile** dysfunction.
AUTHOR: Lea A P; Bryson H M; Balfour J A
CORPORATE SOURCE: Adis International Limited, Auckland, New Zealand.
SOURCE: DRUGS AND AGING, **(1996 Jan)** 8 (1) 56-74. Ref: 123
Journal code: BEK. ISSN: 1170-229X.
PUB. COUNTRY: New Zealand
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611

AB Intracavernous alprostadil (synthetic prostaglandin E1) is a vasodilating agent which acts by relaxing the smooth muscles of the corpus cavernosum and by increasing the diameter of cavernous arteries; this leads to **erection**. Following intracavernous administration, alprostadil is either locally metabolised or rapidly cleared from the penis into the systemic circulation where it is extensively metabolised by the lungs. Studies suggest that long term use of intracavernous alprostadil may increase penile blood flow, although the clinical relevance of this is not currently known. In men with **erectile** dysfunction (ED), short term trials have shown that intracavernous alprostadil is superior or equal, in inducing erections, to other intracavernous agents such as papaverine, the combination of papaverine plus phentolamine, linsidomine and topical nitroglycerin (**glyceryl trinitrate**). Intracavernous alprostadil induced erections in around 70% of patients with ED of various origins in short term studies. 49 to 84% of patients accept the offer of joining self-injection programmes and 13 to 60% of these patients withdraw from such programmes for a variety of reasons. At therapeutic doses, intracavernous alprostadil is well tolerated. The most common adverse event of transient penile pain occurred in around one-third of patients and in 11% of injections, causing 3 to 5% of patients to withdraw from self-injection programmes. Potentially serious adverse events such as priapism and fibrosis occurred in 4 and 8% of patients. Overall, available data suggest that the efficacy of intracavernous alprostadil is superior or equal to that of other erectogenic agents which are in use. Furthermore, the drug is well tolerated especially with regard to serious adverse events. Thus, although further research is necessary to confirm its use in combination with other agents, alprostadil appears likely to become the intracavernous agent of choice for the management of **erectile** dysfunction.

L9 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:129087 BIOSIS
DOCUMENT NUMBER: PREV199698701222
TITLE: Effects of intravenous regional administration of vasodilators; guanethidine, nicardipine, nitroglycerine and **prostaglandin** E-1 in a patient with causalgia.
AUTHOR(S): Mashimo, Takashi (1); Pak, Myon; Inagaki, Yoshimi; Yoshiya, Ikuto
CORPORATE SOURCE: (1) Dep. Anesthesiol., Osaka University Medical School, Yamada-oka 2-2, Suita City, Osaka 565 Japan
SOURCE: Pain Clinic, (1995) Vol. 8, No. 3, pp. 255-261. ISSN: 0169-1112.
DOCUMENT TYPE: Article
LANGUAGE: English

AB We treated a patient with hand causalgia by intravenous regional administration of guanethidine, nicardipine, nitroglycerine and **prostaglandin** E-1 and evaluated the association between the **pain**-relieving effects and changes in the regional skin blood flow and skin temperature as well as the **pain** threshold. **Pain**-relieving effects were observed following intravenous regional administration of these vasodilators, although the degree slightly differed. The reduction in **pain** by guanethidine and nicardipine was well correlated with increases in the regional skin blood flow and temperature, and slightly correlated with elevation of the **pain** threshold, while that by nitroglycerine was well correlated with an increase in skin blood flow but not with changes in the **pain** threshold. The **pain** reduction by **prostaglandin** E-1 was not correlated with changes in the skin blood flow, nor with that in the **pain** threshold. These findings suggest that improvement of regional tissue blood flow is the more determinant factor than a decrease in susceptibility of the nociceptor associated with the effectiveness of guanethidine, nicardipine or nitroglycerine for relieving causalgia **pain**.

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1982:542082 CAPLUS
DOCUMENT NUMBER: 97:142082
TITLE: Role of serotonin and cyclic AMP on facilitation of the fast conducting system activity in the leech Hirudo medicinalis
AUTHOR(S): Belardetti, Francesco; Biondi, Carla; Colombaioni, Laura; Brunelli, Marcello; Trevisani, Agostino
CORPORATE SOURCE: Ist. Fisiol., Univ. Pisa, Pisa, 56100, Italy
SOURCE: Brain Res. (1982), 246(1), 89-103
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the nervous system of H. medicinalis, short-term plastic changes were studied. Depression and facilitation were demonstrated in the fast conducting system (FCS) activity; this pathway consists of a chain of elec. linked neurons present in each ganglion. In semi-intact animals or in prepns. of nerve cord and segments of body wall, both elec. stimulation of peripheral roots and tactile stimulation of the skin induced, after repetitive stimulation (0.1/s), a prolonged decrement of FCS response. Strong **nociceptive** stimulation applied to the head or body wall produced a sustained facilitation of the waned response. The same potentiation was obsd. on perfusing the isolated ganglion with serotonin (5 .times. 10-5M). Such a potentiation was abolished by preincubation with methysergide, an antagonist of serotonin, and with imidazole, a **cAMP phosphodiesterase** activator. Such an effect was mimicked by dibutyryl cAMP. Simultaneous recordings of both T neurons (intracellularly) and FCS firing discharge showed that, during FCS response decrement, the T cell activity remained unchanged and no modification of conductance occurred, excluding therefore a detectable involvement of sensory neurons in the depression. These results suggest that short-term plastic changes of the FCS of the leech are due to a prolonged potentiation of synaptic transmission as a result of a serotonin-mediated increase in cAMP.

L13 ANSWER 3 OF 5 MEDLINE
ACCESSION NUMBER: 95111836 MEDLINE
DOCUMENT NUMBER: 95111836
TITLE: Pharmacological characterization of rabbit corpus cavernosum relaxation mediated by the tissue kallikrein-kinin system.
AUTHOR: Lopes-Martins R A; Antunes E; Oliva M L; Sampaio C A; Burton J; de Nucci G
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medical Sciences, UNICAMP, Campinas (SP), Brazil.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, **(1994 Sep)** 113 (1) 81-6.
Journal code: B00. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504

AB 1. The roles of the tissue kallikrein-kinin system and nitric oxide (NO) release in Phoneutria nigriventer venom-induced relaxations of rabbit corpus cavernosum (RbCC) smooth muscle have been investigated by use of a bioassay cascade. 2. Phoneutria nigriventer venom (10-30 micrograms), porcine pancreatic kallikrein (100 mu), rabbit urinary kallikrein (10 mu), bradykinin (BK, 0.3-3 nmol), acetylcholine (ACh, 0.3-30 nmol) and **glyceryl trinitrate** (GTN, 0.5-10 nmol) caused relaxations of the RbCC strips. Captopril (1 microM) substantially potentiated Phoneutria nigriventer venom- and BK-induced RbCC relaxations without affecting those elicited by GTN. 3. The bradykinin B2 receptor antagonist, Hoe 140 (D-Arg-[Hyp3,Thi5,D- Tic7,Oic8]-BK, 50 nM), aprotinin (10 micrograms ml-1) and the tissue kallikrein inhibitor, Pro-Phe-Aph-Ser-Val- Gln-NH2 (KIZD-06, 1.3 microM) significantly inhibited Phoneutria nigriventer venom-induced RbCC relaxations, without affecting those provoked by GTN and ACh. The B1 receptor antagonist, [Leu9]des Arg10BK (0.5 microM) and soybean trypsin inhibitor (SBTI, 10 micrograms ml-1) had no effect on Phoneutria nigriventer venom-induced RbCC relaxations. 4. The relaxations induced by Phoneutria nigriventer venom, porcine pancreas kallikrein, BK and ACh were significantly inhibited by N omega-nitro-L-arginine methyl ester (L-NAME, 10 microM) but not by D-NAME (10 microM). L-NAME did not affect GTN-induced relaxations. L-Arginine (300 microM), but not D-arginine (300 microM), significantly reversed the inhibitory effect of L-NAME. 5. Our results indicate that Phoneutria nigriventer venom activates the tissue kallikrein-kininogen-kinin system in RbCC strips leading to NO release and suggest a functional role for this system in penile **erection**.

L13 ANSWER 4 OF 5 MEDLINE
ACCESSION NUMBER: 89230122 MEDLINE
DOCUMENT NUMBER: 89230122
TITLE: Synthetic nitrovasodilators are effective, in vitro, in relaxing penile tissue from impotent men: the findings and their implications.
AUTHOR: Heaton J P
CORPORATE SOURCE: Department of Urology, Faculty of Medicine, Queen's University, Kingston, Ont., Canada..
SOURCE: CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, **(1989 Jan)** 67 (1) 78-81.
Journal code: CJM. ISSN: 0008-4212.
PUB. COUNTRY: Canada
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198908
AB Normal penile **erectile** function is dependent on arterial adequacy, appropriate venous occlusion, neurohumoral factors, and finally the relaxation of penile cavernous trabecular smooth muscle. The present experiments were designed to test whether compounds related to endothelium-derived relaxing factor have a role in penile smooth muscle relaxation and whether this role is preserved in clinically impotent tissue. Isometric tension experiments were conducted using strips of human tissue (appropriately obtained) from patients found to be impotent by clinical criteria. **Glyceryl trinitrate** and isosorbide dinitrate produced maximal relaxations of 66 and 63%, respectively, in tissues contracted with norepinephrine: 50% relaxation was observed at 6 x 10(-7) and 8 x 10(-5) M, respectively. The finding of a relaxant response to synthetic nitrovasodilators in "impotent" tissue implies that (i) complete end organ (smooth muscle) failure is not always, if ever, seen, (ii) endothelium-derived factors probably play a role in **erectile** tissue parallel with their role in other vascular tissues, (iii) more proximal factors may be responsible for clinical impotence, and (iv) synthetic nitrovasodilators may have a role in the therapy of clinical impotence.

L13 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1989:166010 CAPLUS
DOCUMENT NUMBER: 110:166010
TITLE: Preliminary studies, in rabbit penile cavernosal tissue, on the role of synthetic nitrovasodilators in **erectile** response
AUTHOR(S): Heaton, Jeremy P. W.
CORPORATE SOURCE: Fac. Med., Queen's Univ., Kingston, ON, Can.
SOURCE: Curr. Ther. Res. (**1989**), 45(2), 278-84
CODEN: CTCEA9; ISSN: 0011-393X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The relaxation of the smooth muscle of the penile corporal trabecular tissue underlies the **erectile** mechanism. Synthetic nitrovasodilators (**glyceryl trinitrate** and isosorbide dinitrate) were shown to cause relaxation of rabbit penile tissue in vitro. It is hypothesized that this relaxation is analogous to that caused by the in vivo action of endothelium derived relaxing factor, nitric oxide. The results are discussed with respect to the potential use

of nitrovasodilators in the clin. management of **erectile** dysfunction.

L13 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1989:166010 CAPLUS
DOCUMENT NUMBER: 110:166010
TITLE: Preliminary studies, in rabbit penile cavernosal tissue, on the role of synthetic nitrovasodilators in **erectile** response
AUTHOR(S): Heaton, Jeremy P. W.
CORPORATE SOURCE: Fac. Med., Queen's Univ., Kingston, ON, Can.
SOURCE: Curr. Ther. Res. (**1989**), 45(2), 278-84
CODEN: CTCEA9; ISSN: 0011-393X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relaxation of the smooth muscle of the penile corporal trabecular tissue underlies the **erectile** mechanism. Synthetic nitrovasodilators (**glyceryl trinitrate** and isosorbide dinitrate) were shown to cause relaxation of rabbit penile tissue in vitro. It is hypothesized that this relaxation is analogous to that caused by the in vivo action of endothelium derived relaxing factor, nitric oxide. The results are discussed with respect to the potential use of nitrovasodilators in the clin. management of **erectile** dysfunction.

ANSWER 4 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:537946 CAPLUS
DOCUMENT NUMBER: 131:149340
TITLE: Method and composition for treating **erectile** dysfunction
INVENTOR(S): Kock, Nils G.; Lycke, Gerhard
PATENT ASSIGNEE(S): Amsu Ltd., UK
SOURCE: U.S., 6 pp., Cont.-in-part of U. S. Ser. No.317,910, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5942512	A	19990824	US 1995-481609	19950607
US 5843961	A	19981201	US 1995-484546	19950607
US 5849803	A	19981215	US 1995-478982	19950607
US 5886039	A	19990323	US 1995-485041	19950607

PRIORITY APPLN. INFO.:
SE 1988-3097 19880902
US 1988-244407 19880914
US 1992-965688 19921022
US 1994-317910 19941004
SE 1988-3087 19880902

AB Disclosed are lipophilic active substance compn. and its use in a new method of treating **erectile** dysfunction by administration thereof, optionally together with a hydrophilic vehicle and optionally an antibacterial agent into the urethra. The invention pharmaceutical compn. comprises (1) a first active agent comprising the .alpha.1-receptor blocking agent phentolamine; (2) a second active agent selected from the group consisting of addnl. .alpha.1-receptor blocking agents, nitroglycerin, vasoactive intestinal polypeptide, and **prostaglandins**; and (3) a hydrophilic vehicle in which the first and second active agents are dispersed, wherein the hydrophilic vehicle is suitable for urethral administration and effective to facilitate passage of the first and second active agents through the urethral membrane.

REFERENCE COUNT: 30
REFERENCE(S):
(2) Anon; GB 2095994 1981 CAPLUS
(3) Anon; EP 015658 1983 CAPLUS
(4) Anon; EP 149254 1985 CAPLUS
(5) Anon; DE 3637157 1987 CAPLUS
(6) Anon; EP 266968 1988 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:565436 CAPLUS
DOCUMENT NUMBER: 113:165436
TITLE: Compositions and method for the treatment of **erectile** dysfunction
INVENTOR(S): Kock, Nils G.; Lycke, Gerhard
PATENT ASSIGNEE(S): AMSU Ltd., UK
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 357581	A1	19900307	EP 1989-850282	19890831
EP 357581	B1	19930728		
EP 357581	B2	19980916		
R: ES, GR				
SE 8803087	A	19900303	SE 1988-3087	19880902
SE 463851	B	19910204		
SE 463851	C	19910613		
ZA 8906681	A	19900627	ZA 1989-6681	19890831
ES 2055677	T3	19941101	ES 1989-850282	19890831
WO 9002545	A1	19900322	WO 1989-SE462	19890901
W: AU, DK, FI, JP, NO				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
AU 8941994	A1	19900402	AU 1989-41994	19890901
AU 638414	B2	19930701		
EP 432199	A1	19910619	EP 1989-909891	19890901
EP 432199	B1	19930728		
R: AT, BE, DE, FR, GB, IT, LU, NL, SE				
JP 04501707	T2	19920326	JP 1989-509519	19890901
JP 07091199	B4	19951004		
AT 91886	E	19930815	AT 1989-909891	19890901
CA 1335346	A1	19950425	CA 1989-610172	19890901
DK 9100364	A	19910301	DK 1991-364	19910301
NO 9100828	A	19910430	NO 1991-828	19910301
US 5843961	A	19981201	US 1995-484546	19950607
US 5849803	A	19981215	US 1995-478982	19950607
US 5886039	A	19990323	US 1995-485041	19950607

PRIORITY APPLN. INFO.:

SE 1988-3087	19880902
US 1988-244407	19880914
EP 1989-909891	19890901
WO 1989-SE462	19890901
US 1992-965688	19921022
US 1994-317910	19941004

AB A lipophilic active substance compn. is provided, as is its use in a method for treatment of **erectile** dysfunction by administration of the compn., with optional antibacterial agent, into the urethra. The active substance may be an .alpha.-receptor blocker, VIP, a **prostaglandin**, or nitroglycerin. Thus, a patient was administered, via the urethra, 60 mg of phentolamine; 30-70 min from administration of the active substance, full **erection** was achieved. The effect of compds. of the invention, alone or in combination, in the treatment of impotence in cystectomized patients is tabulated.

L17 ANSWER 1 OF 22 MEDLINE
ACCESSION NUMBER: 96166990 MEDLINE
DOCUMENT NUMBER: 96166990
TITLE: **Glyceryl trinitrate** enhances the adenosine-induced inhibition of platelet responses: a mechanism potentially involved in the in vivo anti-aggregating effects of organic nitrates.
AUTHOR: Anfossi G; Massucco P; Piretto V; Mularoni E; Cavalot F; Mattiello L; Trovati M
CORPORATE SOURCE: Department of Clinical and Biological Sciences, University of Turin, Torino, Italy.
SOURCE: CLINICAL AND EXPERIMENTAL PHARMACOLOGY AND PHYSIOLOGY, **(1995 Nov)** 22 (11) 803-11. Ref: 57
Journal code: DD8. ISSN: 0305-1870.
PUB. COUNTRY: Australia
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606

AB 1. The present study investigated the influence of the organic nitrate **glyceryl trinitrate** (GTN) on the anti-aggregating effects of adenosine. We determined the effects of adenosine, GTN and their combination on platelet responses in platelet-rich plasma and whole blood, and on intracellular levels of 3',5'-cyclic adenosine monophosphate (**cAMP**) and 3',5'-cyclic guanosine monophosphate (**cGMP**). 2. Adenosine inhibited the in vitro platelet aggregation in response to different agonists in a dose-dependent way through an elevation of intraplatelet **cAMP** levels. Effective adenosine concentrations were higher than those detectable under physiological conditions, but very close to levels achieved during myocardial ischaemia or haemorrhagic shock. 3. GTN was able to decrease platelet responses influencing intraplatelet **cGMP** levels. Furthermore, the drug increased the inhibitory effects of adenosine and enhanced its effects on intraplatelet **cAMP** levels. 4. The present data provides further evidence that compounds that increase intraplatelet levels of **cGMP** and **cAMP** act synergistically on the inhibition of platelet aggregability through the influence of increased **cGMP** levels on **cAMP** accumulation. The interplay between GTN and adenosine in the inhibition of platelet function could be effective during nitrate administration in the treatment of acute myocardial ischaemia when blood adenosine levels are significantly increased.

L17 ANSWER 3 OF 22 MEDLINE
ACCESSION NUMBER: 95180658 MEDLINE
DOCUMENT NUMBER: 95180658
TITLE: Effects of forskolin and organic nitrate on aggregation and intracellular cyclic nucleotide content in human platelets.
AUTHOR: Anfossi G; Massucco P; Mularoni E; Cavalot F; Mattiello L; Trovati M
CORPORATE SOURCE: Department of Clinical and Biological Sciences, University of Turin, Ospedale S. Luigi Gonzaga, Orbassano (To), Italy..
SOURCE: GENERAL PHARMACOLOGY, **(1994 Oct)** 25 (6) 1093-100. Journal code: FLK. ISSN: 0306-3623.
PUB. COUNTRY: ENGLAND: United Kingdom Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506

AB 1. The present study investigated the effect of a combination between forskolin, a naturally occurring diterpene which directly activates adenylyl cyclase, and **glyceryl trinitrate** (GTN), which enhances intraplatelet cyclic guanosine monophosphate levels, on human platelet aggregation and intracellular content of cyclic nucleotides 3',5'-cyclic adenosine monophosphate (**cAMP**) and 3',5'-cyclic guanosine monophosphate (**cGMP**). 2. Forskolin inhibited, in a dose-dependent way, platelet aggregation in response to collagen and adrenaline in platelet-rich plasma. In whole blood samples, forskolin inhibited collagen-stimulated aggregation. In presence of forskolin the intraplatelet **cAMP** levels were significantly increased. 3. GTN directly decreased the platelet response to collagen in whole blood samples (IC50 = 122 mumol/l) and it increased the intraplatelet levels of both **cGMP** and **cAMP**. 4. GTN at 20 and 40 mumol potentiated the inhibitory effects of forskolin on platelet aggregation in both platelet-rich plasma and whole blood. 5. Our results suggest a synergistic effect of the simultaneous increase of both **cAMP** and **cGMP** on the biochemical steps involved in the inhibition of the platelet response.

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L17 ANSWER 4 OF 22 MEDLINE
ACCESSION NUMBER: 94134812 MEDLINE
DOCUMENT NUMBER: 94134812
TITLE: Organic nitrates and compounds that increase intraplatelet cyclic guanosine monophosphate (**cGMP**) levels enhance the antiaggregating effects of the stable prostacyclin analogue iloprost.
AUTHOR: Anfossi G; Massucco P; Mularoni E; Cavalot F; Mattiello L; Trovati M
CORPORATE SOURCE: Department of Clinical and Biological Sciences, University of Turin Ospedale S. Luigi Gonzaga, Orbassano Torino, Italy.
SOURCE: PROSTAGLANDINS LEUKOTRIENES AND ESSENTIAL FATTY ACIDS, **(1993 Nov)** 49 (5) 839-45.
Journal code: P04. ISSN: 0952-3278.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199405

AB The present study investigated the effect of a combination between the stable prostacyclin (PGI2) analogue iloprost and compounds, **glyceryl trinitrate** (GTN) and L-arginine-, which enhance the intraplatelet cyclic guanosine monophosphate (**cGMP**) levels on platelet aggregation, release reaction and cyclic nucleotide content: in particular cyclic adenosine monophosphate (**cAMP**) and **cGMP**. Iloprost inhibited in a dose-dependent way the platelet aggregation in response to collagen, adenosine diphosphate (ADP) and adrenaline and it increased the intraplatelet **cAMP** concentrations. GTN directly decreased the platelet responses and increased the intraplatelet levels of both **cGMP** and **cAMP**. GTN (20 x 10(-6) mol/l) and L-arginine (0.2 x 10(-3) mol/l) potentiated the inhibitory effects of iloprost on platelet aggregation and release reaction. Our results suggest: 1. A synergistic effect of the simultaneous increase of both **cAMP** and **cGMP** on the biochemical steps involved in the inhibition of the platelet response; 2. An influence of **cGMP** on **cAMP** accumulation.

ANSWER 15 OF 16 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1995:400628 CAPLUS

DOCUMENT NUMBER: 122:208312

TITLE: Characterization of cyclic nucleotide phosphodiesterases with cyclic AMP analogs: topology of the catalytic sites and comparison with other cyclic AMP-binding proteins

AUTHOR(S): Butt, Elke; Beltman, Jerlyn; Becker, Donna E.; Jensen, Gregory S.; Rybalkin, Sergei D.; Jastorff, Bernd; Beavo, Joseph A.

CORPORATE SOURCE: Dep. Pharmacology, Univ. Washington, Seattle, WA, 98195, USA

SOURCE: Mol. Pharmacol. (**1995**), 47(2), 340-7
CODEN: MOPMA3; ISSN: 0026-895X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To define essential interactions of **cAMP** with the catalytic sites of cyclic nucleotide phosphodiesterases (PDEs) and to begin to map the topol. of the sites, the authors have tested a series of **cAMP** analogs as competitive inhibitors of the PDEs that hydrolyze **cAMP** with high efficiency (PDE1, PDE2, **PDE3**, and PDE4). Comparisons of IC50 values, relative to **cAMP**, were used to predict which functional groups on **cAMP** interact with each isoenzyme. Common to all PDEs tested, except for the calcium/calmodulin-dependent PDE (CaM-PDE, PDE1), is an interaction at the N1-position of **cAMP** and a distinct lack of binding to the 2'-hydroxyl group of the ribose moiety. Only the **cGMP**-stimulated (PDE2) and **cAMP**-specific (PDE4) PDEs appear to interact strongly at the N7-position. The **cGMP**-inhibited PDE (cGI-PDE, **PDE3**) may interact less strongly with this nitrogen. The PDE4 and **PDE3** both interact with **cAMP** through the 6-amino group, which most likely serves as a hydrogen bond donor. PDE4 and **PDE3** appear to be able to bind to the anti-conformer of **cAMP**, whereas the PDE1 and PDE2 bind the syn-conformer. The CaM-PDE exhibits no appreciable specificity for any of the analogs tested, showing little or no interaction with the 6-amino group or with any of the ring nitrogens. Large differences exist in the nucleotide-binding requirements for the PDE catalytic sites, compared with the regulatory sites of **cAMP**-dependent protein kinase and the catabolite activator protein.

L6 ANSWER 23 OF 29 MEDLINE
ACCESSION NUMBER: 96091822 MEDLINE
DOCUMENT NUMBER: 96091822
TITLE: Effects of papaverine and vasointestinal polypeptide on penile and vascular **cAMP** and **cGMP** in control and diabetic animals: an in vitro study.
AUTHOR: Miller M A; Morgan R J; Thompson C S; Mikhailidis D P; Jeremy J Y
CORPORATE SOURCE: Department of Urology, Royal Free Hospital Trust and Medical School, London, UK.
SOURCE: INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, (1995 Jun) 7 (2) 91-100.
Journal code: BUX. ISSN: 0955-9930.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
AB Adenosine 3'5'-cyclic monophosphate (**cAMP**) and guanosine 3'5'-cyclic monophosphate (**cGMP**) mediate penile **erection**. We have previously established that adenylate and guanylate cyclase activity is elevated in the diabetic rat penis and aorta. This study investigates the action of papaverine and vasoactive intestinal polypeptide (VIP) on these cyclases. The aortae and penes of Sprague Dawley rats (n = 7) were stimulated with VIP and papaverine. Diabetes mellitus (DM) was induced in Sprague Dawley rats (n = 7) with streptozotocin and the penile and aortic tissues were treated with VIP. The penes, aortae and carotid arteries of New Zealand White rabbits were similarly processed. **cAMP** and **cGMP** generation was measured by radioimmunoassay. In all tissues: VIP stimulated **cAMP** synthesis; VIP did not increase **cGMP** levels; papaverine was without effect on either **cAMP** or **cGMP** synthesis. VIP-stimulated **cAMP** was significantly enhanced in the diabetic rat penis and aorta; there was also a significant elevation in the basal levels of **cGMP** in these tissues. These data: (1) consolidate that **cAMP** is a mediator of penile **erection**, (2) indicate that papaverine and VIP elicit **erection** by different mechanisms, (3) suggest that an enhanced penile capacity to generate **cAMP** in DM may constitute an adaptive response to counteract the previously reported reduction in VIP content and VIP receptors, and (4) indicate that the penile and vascular tissues of the rabbit respond in a similar manner to VIP and papaverine.

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L6 ANSWER 26 OF 29 MEDLINE
ACCESSION NUMBER: 93204310 MEDLINE
DOCUMENT NUMBER: 93204310
TITLE: The role of cyclic adenosine monophosphate, cyclic guanosine monophosphate, endothelium and nonadrenergic, noncholinergic neurotransmission in canine penile **erection**.
AUTHOR: Trigo-Rocha F; Hsu G L; Donatucci C F; Lue T F
CORPORATE SOURCE: Department of Urology, University of California School of Medicine, San Francisco..
CONTRACT NUMBER: RO 1 HD 19640 (NICHD)
SOURCE: JOURNAL OF UROLOGY, (1993 Apr) 149 (4) 872-7.
Journal code: KC7. ISSN: 0022-5347.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199306

AB To elucidate the neuropharmacology of **erection**, we undertook an in vivo canine study to examine the role of cholinergic and nonadrenergic, noncholinergic (NANC) neuroeffectors and the sinusoidal endothelium in **erection** induced by electrostimulation. We also examined the effect of adenylate cyclase and guanylate cyclase blockers by intravenous injection of N-ethylmaleimide and methylene blue, respectively. In addition, the effects of intracavernous injection of the nitric oxide-releasing substance, nitroprusside, and bromocyclic adenosine monophosphate (AMP) and bromocyclic guanosine monophosphate (GMP) were also studied. In contrast to in vitro results, atropine reduced the increase of intracavernous pressure after neurostimulation ($p = 0.029$). Intracavernous injection of CHAPS to destroy the sinusoidal endothelium abolished the response to acetylcholine ($p = 0.001$), but only partially inhibited the response to electrostimulation (mean = 75% pressure increase, $p = 0.022$), indicating that neuronal nitric oxide plays a major role in penile **erection**. Methylene blue, a guanylate cyclase inhibitor, significantly inhibited the **erectile** response to both neurostimulation and sodium nitroprusside ($p = 0.000$ and 0.017, respectively). However, N-ethylmaleimide, an adenylate cyclase inhibitor, could not reduce the response to neurostimulation ($p = 0.078$). The **erectile** response to intracavernous injection of **cGMP** was significantly better than that induced by **cAMP** ($p = 0.025$). Our results suggest that both the cholinergic and NANC neuroeffectors and the sinusoidal endothelium are involved in **erection**. In addition, our data imply that the neuronal nitric oxide/cyclic GMP system is the most likely pathway for penile smooth muscle relaxation and **erection**.

L6 ANSWER 29 OF 29 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1989:37188 CAPLUS
DOCUMENT NUMBER: 110:37188
TITLE: Characterization of cyclic nucleotide and inositol 1,4,5-trisphosphate-sensitive calcium-exchange activity of smooth muscle cells cultured from the human corpora cavernosa
AUTHOR(S): Krall, J. Frederick; Fittingoff, Marianne; Rajfer, Jacob
CORPORATE SOURCE: Veterans Adm. Med. Cent., Sepulveda, CA, 91343, USA
SOURCE: Biol. Reprod. (1988), 39(4), 913-22
CODEN: BIREBV; ISSN: 0006-3363
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Corpus cavernosum tissue from a potent man was grown in cell culture. The cells grew as noncontractile cultures, but had the following smooth muscle cell properties: they expressed desmin, the muscle cell-specific intermediate filament protein. They accumulated 45Ca2+ from the medium, which was released by exposure to the ionophore A 23187, to cyclic nucleotides (**cGMP** .mchgt. **cAMP**), and to the phosphodiesterase inhibitor papaverine; and they accumulated Ca2+ in an ATP-dependent manner when the cultured cells were permeabilized by digitonin extn. ATP-dependent Ca2+ uptake was inhibited .apprx.80% by ruthenium red and stimulated by **cGMP** (.mchgt. **cAMP**). Inositol 1,4,5-trisphosphate (IP3), which is thought to mediate the release of Ca2+ by the smooth muscle cell sarcoplasmic reticulum in vivo, released .apprx.0.85 pmol Ca2+/106 cells from the digitonin-extd. cells. IP3-dependent release occurred in the presence of ruthenium red and was not affected by **cGMP** or **cAMP**. Apparently, smooth muscle from this human source can be grown successfully in cell culture, and the biochem. pathways that regulate tension in vivo may be perpetuated in vitro. Moreover, some of the clin. responses to drugs administered in situ for **erectile** dysfunction (e.g., papaverine) may be the result of altered cavernosal smooth muscle cell Ca2+ exchange and may be mediated by **cGMP**.